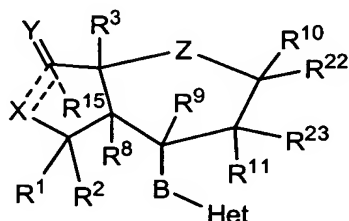


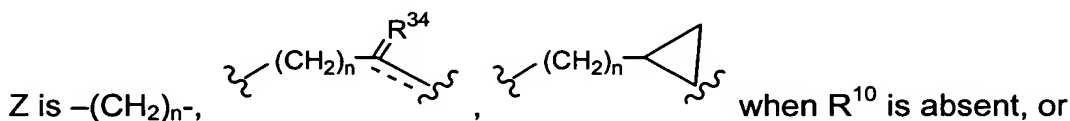
5 We claim:

1. A method of treating a therapeutic condition comprising administering to a mammal in need of such treatment an effective amount of at least one compound of the formula:

10




or a pharmaceutically acceptable isomer, salt, solvate or co-crystal form thereof, wherein:



15



the single dotted line adjacent to R^{34}  represents an optional double bond;

the double dotted lines adjacent to X  together represent an optional single bond;

20

n is 0-2;

R^1 and R^2 are independently selected from the group consisting of H, C₁-C₆ alkyl, fluoro(C₁-C₆)alkyl, difluoro(C₁-C₆)alkyl, trifluoro-(C₁-C₆)alkyl, C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, aryl(C₁-C₆)alkyl, aryl(C₂-C₆)alkenyl, heteroaryl(C₁-C₆)alkyl, heteroaryl(C₂-C₆)alkenyl, hydroxy-(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, amino-(C₁-C₆)alkyl, aryl and thio(C₁-C₆)alkyl; or R^1 and R^2 together form a =O group;

25

R^3 is H, hydroxy, C₁-C₆ alkoxy, $-NR^{18}R^{19}$, $-SOR^{16}$, $-SO_2R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{18}R^{19}$, C₁-C₆ alkyl, halogen, fluoro(C₁-C₆)alkyl, difluoro(C₁-C₆)alkyl, trifluoro(C₁-C₆)alkyl, C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, aryl(C₁-C₆)alkyl, aryl(C₂-

- 5 C₆)alkenyl, heteroaryl(C₁-C₆)alkyl, heteroaryl(C₂-C₆)alkenyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, aryl, thio(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl or (C₁-C₆)alkylamino(C₁-C₆)alkyl;
- R³⁴ is (H, R³), (H, R⁴³), =O or =NOR¹⁷ when the optional double bond adjacent to R³⁴ is absent; R³⁴ is R⁴⁴ when the double bond is present;
- 10 Het is a mono-, bi- or tricyclic heteroaromatic group of 5 to 14 atoms comprised of 1 to 13 carbon atoms and 1 to 4 heteroatoms independently selected from the group consisting of N, O and S, wherein a ring nitrogen can form an N-oxide or a quaternary group with a C₁-C₄ alkyl group, wherein Het is attached to B by a carbon atom ring member of Het, and wherein the Het group is substituted by
- 15 1 to 4 moieties, W, independently selected from the group consisting of H; C₁-C₆ alkyl; fluoro(C₁-C₆)alkyl; difluoro(C₁-C₆)alkyl; trifluoro-(C₁-C₆)-alkyl; C₃-C₇ cycloalkyl; heterocycloalkyl; heterocycloalkyl substituted by C₁-C₆ alkyl, C₂-C₆ alkenyl, OH-(C₁-C₆)alkyl, or =O; C₂-C₆ alkenyl; R²¹-aryl(C₁-C₆)alkyl; R²¹-aryl-(C₂-C₆)-alkenyl; R²¹-aryloxy; R²¹-aryl-NH-; heteroaryl(C₁-C₆)alkyl; heteroaryl(C₂-
- 20 C₆)-alkenyl; heteroaryloxy; heteroaryl-NH-; hydroxy(C₁-C₆)alkyl; dihydroxy(C₁-C₆)alkyl; amino(C₁-C₆)alkyl; (C₁-C₆)alkylamino-(C₁-C₆)alkyl; di-((C₁-C₆)alkyl)-amino(C₁-C₆)alkyl; thio(C₁-C₆)alkyl; C₁-C₆ alkoxy; C₂-C₆ alkenyloxy; halogen; -NR⁴R⁵; -CN; -OH; -COOR¹⁷; -COR¹⁶; -OSO₂CF₃; -CH₂OCH₂CF₃; (C₁-C₆)alkylthio; -C(O)NR⁴R⁵; -OCHR⁶-phenyl; phenoxy-(C₁-C₆)alkyl; -NHCOR¹⁶; -
- 25 NHSO₂R¹⁶; biphenyl; -OC(R⁶)₂COOR⁷; -OC(R⁶)₂C(O)NR⁴R⁵; (C₁-C₆)alkoxy; -C(=NOR¹⁷)R¹⁸; C₁-C₆ alkoxy substituted by (C₁-C₆)alkyl, amino, -OH, COOR¹⁷, -NHCOOR¹⁷, -CONR⁴R⁵, aryl, aryl substituted by 1 to 3 moieties independently selected from the group consisting of halogen, -CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy and -COOR¹⁷, aryl wherein adjacent carbons form a ring with a methylenedioxy
- 30 group, -C(O)NR⁴R⁵ or heteroaryl; R²¹-aryl; aryl wherein adjacent carbons form a ring with a methylenedioxy group; R⁴¹-heteroaryl; and heteroaryl wherein adjacent carbon atoms form a ring with a C₃-C₅ alkylene group or a methylenedioxy group;

5 R^4 and R^5 are independently selected from the group consisting of H, C₁-C₆ alkyl, phenyl, benzyl and C₃-C₇ cycloalkyl, or R^4 and R^5 together are $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_2NR^7-(CH_2)_2-$ and form a ring with the nitrogen to which they are attached;

R^6 is independently selected from the group consisting of H, C₁-C₆ alkyl, 10 phenyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl and amino(C₁-C₆)alkyl;

R^7 is H or (C₁-C₆)alkyl;

R^8 , R^{10} and R^{11} are independently selected from the group consisting of R^1 and $-OR^1$, provided that when the optional double bond is present, R^{10} is 15 absent;

R^9 is H, OH, C₁-C₆ alkoxy, halogen or halo(C₁-C₆)alkyl;

B is $-(CH_2)_{n3}-$, $-CH_2-O-$, $-CH_2S-$, $-CH_2-NR^6-$, $-C(O)NR^6-$, $-NR^6C(O)-$,

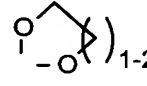
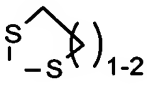
 , cis or trans $-(CH_2)_{n4}CR^{12}=CR^{12a}(CH_2)_{n5}-$ or $-(CH_2)_{n4}C\equiv C(CH_2)_{n5}-$,

wherein n_3 is 0-5, n_4 and n_5 are independently 0-2, and R^{12} and R^{12a} are 20 independently selected from the group consisting of H, C₁-C₆ alkyl and halogen;

X is $-O-$ or $-NR^6-$ when the double dotted lines adjacent to X represent a single bond, or X is H, $-OH$ or $-NHR^{20}$ when the bond is absent;

Y is $=O$, $=S$, (H, H), (H, OH) or (H, C₁-C₆ alkoxy) when the double dotted lines adjacent to X represent a single bond, or when the bond is absent, Y is $=O$, 25 $=NOR^{17}$, (H, H), (H, OH), (H, SH), (H, C₁-C₆ alkoxy) or (H, $-NHR^{45}$);

R^{15} is absent when the double dotted lines adjacent to X represent a single bond; R^{15} is H, C₁-C₆ alkyl, $-NR^{18}R^{19}$ or $-OR^{17}$ when said single bond is absent;

or Y is ₁₋₂ or ₁₋₂ and R^{15} is H or C₁-C₆ alkyl;

R^{16} is C₁-C₆ lower alkyl, phenyl or benzyl;

5 R¹⁷, R¹⁸ and R¹⁹ are independently selected from the group consisting of H, C₁-C₆ alkyl, phenyl, benzyl;

R²⁰ is H, C₁-C₆ alkyl, phenyl, benzyl, -C(O)R⁶ or -SO₂R⁶;

R²¹ is 1 to 3 moieties independently selected from the group consisting of hydrogen, -CN, -CF₃, -OCF₃, halogen, -NO₂, C₁-C₆ alkyl, C₁-C₆alkoxy,
 10 (C₁-C₆)alkylamino, di-((C₁-C₆)alkyl)amino, amino(C₁-C₆)alkyl, (C₁-C₆)-alkylamino(C₁-C₆)alkyl, di-((C₁-C₆)alkyl)-amino(C₁-C₆)alkyl, hydroxy-(C₁-C₆)alkyl, -COOR¹⁷, -COR¹⁷, -NHCOR¹⁶, -NHSO₂R¹⁶, -NHSO₂CH₂CF₃, heteroaryl or -C(=NOR¹⁷)R¹⁸;

R²² and R²³ are independently selected from the group consisting of
 15 hydrogen, R²⁴-(C₁-C₁₀)alkyl, R²⁴-(C₂-C₁₀)alkenyl, R²⁴-(C₂-C₁₀)alkynyl, R²⁷-hetero-cycloalkyl, R²⁵-aryl, R²⁵-aryl(C₁-C₆)alkyl, R²⁹-(C₃-C₇)cycloalkyl, R²⁹-(C₃-C₇)cycloalkenyl, -OH, -OC(O)R³⁰, -C(O)OR³⁰, -C(O)R³⁰, -C(O)NR³⁰R³¹, -NR³⁰R³¹, -NR³⁰C(O)R³¹, -NR³⁰C(O)NR³¹R³², -NHSO₂R³⁰, -OC(O)NR³⁰R³¹, R²⁴-(C₁-C₁₀)alkoxy, R²⁴-(C₂-C₁₀)-alkenyloxy, R²⁴-(C₂-C₁₀)alkynyloxy,
 20 R²⁷-heterocycloalkyloxy, R²⁹-(C₃-C₇)cycloalkyloxy, R²⁹-(C₃-C₇)cyclo-alkenyloxy, R²⁹-(C₃-C₇)cycloalkyl-NH-, -CH₂-O-CH₂-phenyl, -NHSO₂NHR¹⁶ and -CH(=NOR¹⁷);
 or R²² and R¹⁰ together with the carbon to which they are attached, or R²³ and R¹¹ together with the carbon to which they are attached, independently form a R⁴²-substituted carbocyclic ring of 3-10 atoms, or a R⁴²-substituted heterocyclic
 25 ring of 4-10 atoms wherein 1-3 ring members are independently selected from the group consisting of -O-, -NH- and -SO₀₋₂-, provided that when R²² and R¹⁰ form a ring, the optional double bond is absent;

R²⁴ is 1, 2 or 3 moieties independently selected from the group consisting of hydrogen, halogen, -OH, (C₁-C₆)alkoxy, R³⁵-aryl, (C₁-C₁₀)-alkyl-C(O)-, (C₂-C₁₀)-
 30 alkenyl-C(O)-, (C₂-C₁₀)alkynyl-C(O)-, heterocycloalkyl, R²⁶-(C₃-C₇)cycloalkyl, R²⁶-(C₃-C₇)cycloalkenyl, -OC(O)R³⁰, -C(O)OR³⁰, -C(O)R³⁰, -C(O)NR³⁰R³¹, -NR³⁰R³¹, -NR³⁰C(O)R³¹, -NR³⁰C(O)NR³¹R³², -NHSO₂R³⁰, -OC(O)NR³⁰R³¹, R²⁴-(C₂-C₁₀)-alkenyloxy, R²⁴-(C₂-C₁₀)alkynyloxy, R²⁷-heterocycloalkyloxy, R²⁹-(C₃-C₇)-cycloalkyloxy, R²⁹-(C₃-C₇)cyclo-alkenyloxy, R²⁹-(C₃-C₇)cycloalkyl-NH-,
 35 -NHSO₂NHR¹⁶ and -CH(=NOR¹⁷);

5 R^{25} is 1, 2 or 3 moieties independently selected from the group consisting of hydrogen, heterocycloalkyl, halogen, $-\text{COOR}^{36}$, $-\text{CN}$, $-\text{C(O)NR}^{37}\text{R}^{38}$, $-\text{NR}^{39}\text{C(O)R}^{40}$, $-\text{OR}^{36}$, $(\text{C}_3\text{-C}_7)\text{cycloalkyl}$, $(\text{C}_3\text{-C}_7)\text{cycloalkyl-C}_1\text{-C}_6\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkyl}(\text{C}_3\text{-C}_7)\text{cycloalkyl-(C}_1\text{-C}_6\text{alkyl)}$, halo $(\text{C}_1\text{-C}_6)\text{alkyl}(\text{C}_3\text{-C}_7)\text{cycloalkyl}(\text{C}_1\text{-C}_6)\text{alkyl}$, hydroxy $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_1\text{-C}_6)\text{alkyl}$, and R^{41} -heteroaryl; or two R^{25} groups on adjacent ring carbons form a fused methylenedioxy group;

R^{26} is 1, 2, or 3 moieties independently selected from the group consisting of hydrogen, halogen and $(\text{C}_1\text{-C}_6)\text{alkoxy}$;

15 R^{27} is 1, 2 or 3 moieties independently selected from the group consisting of hydrogen, $\text{R}^{28}\text{-(C}_1\text{-C}_{10})\text{alkyl}$, $\text{R}^{28}\text{-(C}_2\text{-C}_{10})\text{alkenyl}$, $\text{R}^{28}\text{-(C}_2\text{-C}_{10})\text{alkynyl}$;

R^{28} is hydrogen, $-\text{OH}$ or $(\text{C}_1\text{-C}_6)\text{alkoxy}$;

R^{29} is 1, 2 or 3 moieties independently selected from the group consisting of hydrogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{OH}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$ and halogen;

20 R^{30} , R^{31} and R^{32} are independently selected from the group consisting of hydrogen, $(\text{C}_1\text{-C}_{10})\text{-alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_1\text{-C}_{10})\text{-alkyl}$, $\text{R}^{25}\text{-aryl}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{R}^{33}\text{-(C}_3\text{-C}_7)\text{cycloalkyl}$, $\text{R}^{34}\text{-(C}_3\text{-C}_7)\text{cycloalkyl}(\text{C}_1\text{-C}_6)\text{alkyl}$, $\text{R}^{25}\text{-aryl}$, heterocycloalkyl, heteroaryl, heterocycloalkyl $(\text{C}_1\text{-C}_6)\text{alkyl}$ and heteroaryl $(\text{C}_1\text{-C}_6)\text{alkyl}$;

R^{33} is hydrogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $\text{OH-(C}_1\text{-C}_6)\text{alkyl}$ or $(\text{C}_1\text{-C}_6)\text{alkoxy}$;

25 R^{35} is 1 to 4 moieties independently selected from the group consisting of hydrogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{OH}$, halogen, $-\text{CN}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, trihalo $(\text{C}_1\text{-C}_6)\text{alkoxy}$, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, di $((\text{C}_1\text{-C}_6)\text{alkyl})\text{amino}$, $-\text{OCF}_3$, $\text{OH-(C}_1\text{-C}_6)\text{alkyl}$, $-\text{CHO}$, $-\text{C(O)}(\text{C}_1\text{-C}_6)\text{-alkylamino}$, $-\text{C(O)di}((\text{C}_1\text{-C}_6)\text{alkyl})\text{amino}$, $-\text{NH}_2$, $-\text{NHC(O)}(\text{C}_1\text{-C}_6)\text{alkyl}$ and $-\text{N}((\text{C}_1\text{-C}_6)\text{alkyl})\text{C(O)}(\text{C}_1\text{-C}_6)\text{alkyl}$;

30 R^{36} is hydrogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, halo $(\text{C}_1\text{-C}_6)\text{alkyl}$, dihalo $(\text{C}_1\text{-C}_6)\text{alkyl}$ or trifluoro $(\text{C}_1\text{-C}_6)\text{alkyl}$;

R^{37} and R^{38} are independently selected from the group consisting of hydrogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, aryl $(\text{C}_1\text{-C}_6)\text{alkyl}$, phenyl and $(\text{C}_3\text{-C}_{15})\text{cycloalkyl}$, or R^{37} and R^{38} together are $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$ or $-(\text{CH}_2)_2\text{-NR}^{39}\text{-(CH}_2)_2-$ and form a ring with the nitrogen to which they are attached;

35 R^{39} and R^{40} are independently selected from the group consisting of hydrogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, aryl $(\text{C}_1\text{-C}_6)\text{alkyl}$, phenyl and $(\text{C}_3\text{-C}_{15})\text{-cycloalkyl}$, or R^{39} and

5 R^{40} in the group $-NR^{39}C(O)R^{40}$, together with the carbon and nitrogen atoms to which they are attached, form a cyclic lactam having 5-8 ring members;

R^{41} is 1 to 4 moieties independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkylamino, di $((C_1-C_6)$ alkyl)amino, $-OCF_3$, $OH-(C_1-C_6)$ alkyl, $-CHO$ and phenyl;

10 R^{42} is 1 to 3 moieties independently selected from the group consisting of hydrogen, $-OH$, (C_1-C_6) alkyl and (C_1-C_6) alkoxy;

R^{43} is $-NR^{30}R^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}C(O)NR^{31}R^{32}$, $-NHSO_2R^{30}$ or $-NHCOOR^{17}$;

R^{44} is H, C_1-C_6 alkoxy, $-SOR^{16}$, $-SO_2R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{18}R^{19}$,
15 C_1-C_6 alkyl, halogen, fluoro (C_1-C_6) alkyl, difluoro (C_1-C_6) alkyl, trifluoro (C_1-C_6) alkyl, C_3-C_7 cycloalkyl, C_2-C_6 alkenyl, aryl (C_1-C_6) alkyl, aryl (C_2-C_6) alkenyl, heteroaryl (C_1-C_6) alkyl, heteroaryl (C_2-C_6) alkenyl, hydroxy (C_1-C_6) alkyl, amino (C_1-C_6) alkyl, aryl, thio (C_1-C_6) alkyl, (C_1-C_6) alkoxy (C_1-C_6) alkyl or (C_1-C_6) alkylamino (C_1-C_6) alkyl; and

20 R^{45} is H, C_1-C_6 alkyl, $-COOR^{16}$ or $-SO_2$,

wherein said therapeutic condition is a cardiovascular or circulatory disease or condition, an inflammatory disease or condition, a respiratory tract disease or condition, cancer, acute renal failure, glomerulonephritis, astrogliosis, a fibrotic disorder of the liver, kidney, lung or intestinal tract, Alzheimer's disease, diabetes,
25 diabetic neuropathy, rheumatoid arthritis, neurodegenerative disease, neurotoxic disease, systemic lupus erythematosus, multiple sclerosis, osteoporosis, glaucoma, macular degeneration, psoriasis, radiation fibrosis, endothelial dysfunction, a wound or a spinal cord injury, or a symptom or result thereof.

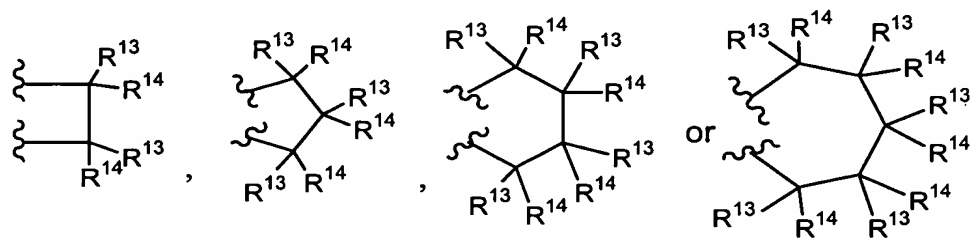
30 2. The method of claim 1 wherein the cardiovascular or circulatory disease or condition is atherosclerosis, restenosis, hypertension, acute coronary syndrome, angina pectoris, arrhythmia, heart disease, heart failure, myocardial infarction, thrombotic or thromboembolytic stroke, a peripheral vascular disease, deep vein thrombosis, venous thromboembolism, a
35 cardiovascular disease associated with hormone replacement therapy, disseminated intravascular coagulation syndrome, renal ischemia, cerebral

- 5 stroke, cerebral ischemia, cerebral infarction, migraine, renal vascular homeostasis or erectile dysfunction.
3. The method of claim 1 wherein the inflammatory disease or condition is irritable bowel syndrome, Crohn's disease, nephritis or a radiation- or
10 chemotherapy- induced proliferative or inflammatory disorder of the gastrointestinal tract, lung, urinary bladder, gastrointestinal tract or other organ.
4. The method of claim 1 wherein the respiratory tract disease or condition is reversible airway obstruction, asthma, chronic asthma, bronchitis or chronic
15 airways disease.
5. The method of claim 1 wherein the cancer is renal cell carcinoma or an angiogenesis related disorder.
20
6. The method of claim 1 wherein the neurodegenerative disease is Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease or Wilson's disease.
- 25 7. The method of claim 1 further comprising administering at least one therapeutically effective agent useful in the treatment of inflammation, rheumatism, asthma, glomerulonephritis, osteoporosis, neuropathy and/or malignant tumors, angiogenesis related disorders, cancer, disorders of the liver, kidney or lung, melanoma, renal cell carcinoma, renal disease, acute
30 renal failure, chronic renal failure, renal vascular homeostasis, glomerulonephritis, chronic airways disease, bladder inflammation, neurodegenerative and/or neurotoxic diseases, conditions, or injuries, radiation fibrosis, endothelial dysfunction, periodontal diseases or wounds.
- 35 8. The method of claim 7 further comprising administering at least two therapeutically effective agents.

-

- the single dotted line adjacent to R¹⁰ ----- represents an optional double

- Q is



- R¹ and R² are independently selected from the group consisting of H,
 20 (C₁-C₆)alkyl, fluoro(C₁-C₆)alkyl-, difluoro(C₁-C₆)alkyl-, trifluoro-(C₁-C₆)alkyl-,
 (C₃-C₆)cycloalkyl, (C₂-C₆)alkenyl, hydroxy-(C₁-C₆)alkyl-, and amino(C₁-C₆)alkyl-;
 R³ is H, hydroxy, (C₁-C₆)alkoxy, -SOR¹⁶, -SO₂R¹⁷, -C(O)OR¹⁷,
 -C(O)NR¹⁸R¹⁹, -(C₁-C₆)alkyl-C(O)NR¹⁸R¹⁹, (C₁-C₆)alkyl, halogen,
 fluoro(C₁-C₆)alkyl-, difluoro(C₁-C₆)alkyl-, trifluoro(C₁-C₆)alkyl-, (C₃-C₆)cycloalkyl,
 25 (C₃-C₆)-cycloalkyl-(C₁-C₆)alkyl-, (C₂-C₆)alkenyl, aryl(C₁-C₆)alkyl-,
 aryl(C₂-C₆)alkenyl-, heteroaryl(C₁-C₆)alkyl-, heteroaryl(C₂-C₆)alkenyl-,
 hydroxy(C₁-C₆)-alkyl-, -NR²²R²³, NR²²R²³-(C₁-C₆)alkyl-, aryl, thio(C₁-C₆)alkyl-,

5 (C₁-C₆)alkyl-thio(C₁-C₆)alkyl-, (C₁-C₆)alkoxy(C₁-C₆)alkyl-,
NR¹⁸R¹⁹-C(O)-(C₁-C₆)alkyl- or (C₃-C₆)cycloalkyl-(C₁-C₆)alkyl-;

Het is a mono- or bi-cyclic heteroaryl group of 5 to 10 atoms comprised of 1
to 9 carbon atoms and 1 to 4 heteroatoms independently selected from the group
consisting of N, O and S, wherein a ring nitrogen can form an N-oxide or a
10 quaternary group with a (C₁-C₄)alkyl group, wherein Het is attached to B by a
carbon atom ring member of said Het, and wherein the Het group is substituted by
W;

W is 1 to 4 moieties independently selected from the group consisting of H,
(C₁-C₆)alkyl, fluoro(C₁-C₆)alkyl-, difluoro(C₁-C₆)alkyl-, trifluoro(C₁-C₆)alkyl-,
15 (C₃-C₆)cycloalkyl, hydroxy(C₁-C₆)alkyl-, dihydroxy(C₁-C₆)alkyl-,
NR²⁵R²⁶(C₁-C₆)alkyl-, thio(C₁-C₆)alkyl-, -OH, (C₁-C₆)alkoxy, halogen, -NR⁴R⁵,
-C(O)OR¹⁷, -COR¹⁶, (C₁-C₆)alkylthio-, R²¹-aryl, R²¹-aryl(C₁-C₆)alkyl-, aryl wherein
adjacent ring carbons in said aryl, along with two O atoms, form a methylenedioxy
group, and R²¹-heteroaryl;

20 R⁴ and R⁵ are independently selected from the group consisting of H,
(C₁-C₆)alkyl, phenyl, benzyl and (C₃-C₆)cycloalkyl, or R⁴ and R⁵ taken together are
-(CH₂)₄-, -(CH₂)₅- or -(CH₂)₂NR⁷-(CH₂)₂- and form a ring with the nitrogen to
which they are attached;

R⁶ is H, (C₁-C₆)alkyl or phenyl;

25 R⁷ is H, (C₁-C₆)alkyl, -C(O)-R¹⁶, -C(O)OR¹⁷ or -S(O)₂R¹⁷;

R⁸, R¹⁰ and R¹¹ are independently selected from the group consisting of R¹
and -OR¹, provided that when the optional double bond shown in Formula II is
present, R¹⁰ is absent;

R⁹ is H, OH or (C₁-C₆)alkoxy;

30 B is -(CH₂)_{n3}-, cis or trans -(CH₂)_{n4}CR¹²=CR^{12a}(CH₂)_{n5}- or
-(CH₂)_{n4}C≡C(CH₂)_{n5}-, wherein n₃ is 0-5, n₄ and n₅ are independently 0-2, and R¹²
and R^{12a} are independently selected from the group consisting of H, (C₁-C₆)alkyl
and halogen;

X is -O- or -NR⁶- when the dotted line shown adjacent to X in Formula II
35 represents a single bond, or X is -OH or -NHR²⁰ when the bond is absent;

5 Y is =O, =S, (H, H), (H, OH) or (H, (C₁-C₆)alkoxy) when the dotted line shown adjacent to X in Formula II represents a single bond, or when the bond is absent, Y is =O, (H, H), (H, OH), (H, SH) or (H, (C₁-C₆)alkoxy);

each R¹³ is independently selected from H, (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, -(CH₂)_{n6}NHC(O)OR^{16b}, -(CH₂)_{n6}NHC(O)R^{16b}, -(CH₂)_{n6}NHC(O)NR⁴R⁵,
10 -(CH₂)_{n6}NHSO₂R¹⁶, -(CH₂)_{n6}NHSO₂NR⁴R⁵, and -(CH₂)_{n6}C(O)NR²⁸R²⁹ where n₆ is 0-4, haloalkyl, and halogen;

each R¹⁴ is independently selected from H, (C₁-C₆)alkyl, -OH, (C₁-C₆)alkoxy, R²⁷-aryl(C₁-C₆)alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -(CH₂)_{n6}NHC(O)OR^{16b}, -(CH₂)_{n6}NHC(O)R^{16b},
15 -(CH₂)_{n6}NHC(O)NR⁴R⁵, -(CH₂)_{n6}NHSO₂R¹⁶, -(CH₂)_{n6}NHSO₂NR⁴R⁵, and -(CH₂)_{n6}C(O)NR²⁸R²⁹ where n₆ is 0-4, halogen and haloalkyl; or

R¹³ and R¹⁴ taken together form a spirocyclic or a heterospirocyclic ring of 3-6 atoms;

wherein at least one of R¹³ or R¹⁴ is selected from the group consisting of
20 -(CH₂)_{n6}NHC(O)OR^{16b}, -(CH₂)_{n6}NHC(O)R^{16b}, -(CH₂)_{n6}NHC(O)NR⁴R⁵, -(CH₂)_{n6}NHSO₂R¹⁶, -(CH₂)_{n6}NHSO₂NR⁴R⁵, and -(CH₂)_{n6}C(O)NR²⁸R²⁹ where n₆ is 0-4;

R¹⁵ is H when the double dotted line shown adjacent to X in Formula II represents a single bond and is H, (C₁-C₆)alkyl, -NR¹⁸R¹⁹, or -OR¹⁷ when said
25 bond is absent;

R¹⁶ is independently selected from the group consisting of (C₁-C₆)alkyl, phenyl and benzyl;

R^{16b} is H, alkoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl-, R²²-O-C(O)-(C₁-C₆)alkyl-, (C₃-C₆)cycloalkyl, R²¹-aryl, R²¹-aryl(C₁-C₆)alkyl, haloalkyl, alkenyl, halosubstituted alkenyl, alkynyl, halosubstituted alkynyl,
30 R²¹-heteroaryl, R²¹-(C₁-C₆)alkyl heteroaryl, R²¹-(C₁-C₆)alkyl heterocycloalkyl, R²⁸R²⁹N-(C₁-C₆)alkyl, R²⁸R²⁹N-(CO)-(C₁-C₆)alkyl, R²⁸R²⁹N-(CO)O-(C₁-C₆)alkyl, R²⁸O(CO)N(R²⁹)-(C₁-C₆)alkyl, R²⁸S(O)₂N(R²⁹)-(C₁-C₆)alkyl, R²⁸R²⁹N-(CO)-N(R²⁹)-(C₁-C₆)alkyl, R²⁸R²⁹N-S(O)₂N(R²⁹)-(C₁-C₆)alkyl,

5 $R^{28}-(CO)N(R^{29})-(C_1-C_6)alkyl$, $R^{28}R^{29}N-S(O)_2-(C_1-C_6)alkyl$, $HOS(O)_2-(C_1-C_6)alkyl$, $(OH)_2P(O)_2-(C_1-C_6)alkyl$, $R^{28}-S-(C_1-C_6)alkyl$, $R^{28}-S(O)_2-(C_1-C_6)alkyl$ or hydroxy $(C_1-C_6)alkyl$;

R^{17} , R^{18} and R^{19} are independently selected from the group consisting of H, $(C_1-C_6)alkyl$, phenyl, and benzyl;

10 R^{20} is H, $(C_1-C_6)alkyl$, phenyl, benzyl, $-C(O)R^6$ or $-S(O)_2R^6$;

R^{21} is 1 to 3 moieties independently selected from the group consisting of H, $-CN$, $-CF_3$, $-OCF_3$, halogen, $-NO_2$, $(C_1-C_6)alkyl$, $-OH$, $(C_1-C_6)alkoxy$, $(C_1-C_6)-alkylamino-$, di- $((C_1-C_6)alkyl)amino-$, $NR^{25}R^{26}-(C_1-C_6)alkyl-$, hydroxy- $(C_1-C_6)alkyl-$, $-C(O)OR^{17}$, $-C(O)R^{17}$, $-NHC(O)R^{16}$, $-NHS(O)_2R^{16}$,

15 $-NHS(O)_2CH_2CF_3$, $-C(O)NR^{25}R^{26}$, $-NR^{25}-C(O)-NR^{25}R^{26}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$ and $-SR^{13}$;

R^{22} is H or $(C_1-C_6)alkyl$;

R^{23} is H, $(C_1-C_6)alkyl$, $-C(O)R^{24}$, $-S(O)_2R^{24}$, $-C(O)NHR^{24}$ or $-S(O)_2NHR^{24}$;

R^{24} is $(C_1-C_6)alkyl$, hydroxy $(C_1-C_6)alkyl$ or $NR^{25}R^{26}-((C_1-C_6)alkyl)-$;

20 R^{25} and R^{26} are independently selected from the group consisting of H and $(C_1-C_6)alkyl$;

R^{27} is 1, 2 or 3 moieties selected from the group consisting of H, $(C_1-C_6)alkyl$, $(C_3-C_6)cycloalkyl$, $(C_1-C_6)alkoxy$, halogen and $-OH$; and

25 R^{28} and R^{29} are independently selected from the group consisting of H, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $R^{27}-aryl(C_1-C_6)alkyl$, heteroaryl, heteroarylalkyl, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, heterocyclyl, heterocyclylalkyl, and haloalkyl; or

R^{28} and R^{29} taken together form a spirocyclic or a heterospirocyclic ring of 3-6 atoms,

30 wherein said therapeutic condition is a cardiovascular or circulatory disease or condition, an inflammatory disease or condition, a respiratory tract disease or condition, cancer, acute renal failure, glomerulonephritis, astrogliosis, a fibrotic disorder of the liver, kidney, lung or intestinal tract, Alzheimer's disease, diabetes, diabetic neuropathy, rheumatoid arthritis, neurodegenerative disease, neurotoxic
35 disease, systemic lupus erythematosus, multiple sclerosis, osteoporosis,

- 5 glaucoma, macular degeneration, psoriasis, radiation fibrosis, endothelial
dysfunction, a wound or a spinal cord injury, or a symptom or result thereof.
10. The method of claim 9 wherein the cardiovascular or circulatory disease or
condition is atherosclerosis, restenosis, hypertension, acute coronary
10 syndrome, angina pectoris, arrhythmia, heart disease, heart failure,
myocardial infarction, thrombotic or thromboembolytic stroke, a peripheral
vascular disease, deep vein thrombosis, venous thromboembolism, a
cardiovascular disease associated with hormone replacement therapy,
disseminated intravascular coagulation syndrome, renal ischemia, cerebral
15 stroke, cerebral ischemia, cerebral infarction, migraine, renal vascular
homeostasis or erectile dysfunction.
11. The method of claim 9 wherein the inflammatory disease or condition is
irritable bowel syndrome, Crohn's disease, nephritis or a radiation- or
20 chemotherapy- induced proliferative or inflammatory disorder of the
gastrointestinal tract, lung, urinary bladder, gastrointestinal tract or other
organ.
12. The method of claim 9 wherein the respiratory tract disease or condition is
25 reversible airway obstruction, asthma, chronic asthma, bronchitis or chronic
airways disease.
13. The method of claim 9 wherein the cancer is renal cell carcinoma or an
angiogenesis related disorder.
- 30 14. The method of claim 9 wherein the neurodegenerative disease is
Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease,
Huntington's disease or Wilson's disease.
- 35 15. The method of claim 9 further comprising administering at least one
therapeutically effective agent useful in the treatment of inflammation,

- 5 rheumatism, asthma, glomerulonephritis, osteoporosis, neuropathy and/or
 malignant tumors, angiogenesis related disorders, cancer, disorders of the
 liver, kidney or lung, melanoma, renal cell carcinoma, renal disease, acute
 renal failure, chronic renal failure, renal vascular homeostasis,
 glomerulonephritis, chronic airways disease, bladder inflammation,
10 neurodegenerative and/or neurotoxic diseases, conditions, or injuries,
 radiation fibrosis, endothelial dysfunction, periodontal diseases or wounds.
16. The method of claim 15 further comprising administering at least two
 therapeutically effective agents.

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